

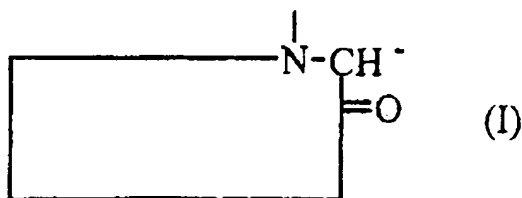
AMENDMENTS TO THE CLAIMS:


Please amend claims 1, 4, 8, 13-14, and 23, cancel claims 2 and 22, and add claim 24 as indicated below. The following complete list of claims replaces all earlier versions of the claims in this application.

1. (Currently Amended) A process for preparing a polyanion for use as an intermediate in the preparation of a cyclosporin derivative, said process comprising treating a cyclosporin with a hexamethyldisilazane metal salt and a metal halide.

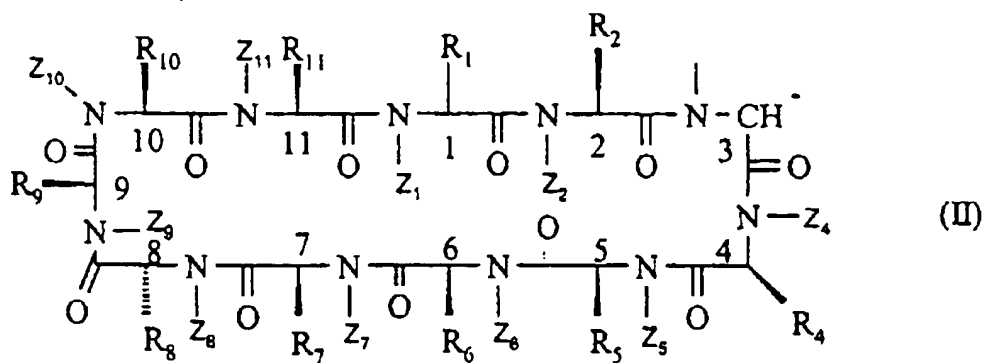
2. (Cancelled)

3. (Original) The process according to claim 1, in which said polyanion has the formula:



in which  is a cyclosporin in which one or more hydroxyl groups and optionally one or more non-methylated nitrogen atoms at the α position and optionally any other deprotonatable acidic group are optionally deprotonated or in the protected form.

4. (Currently Amended) The process according to claim 1, in which said polyanion has the formula:



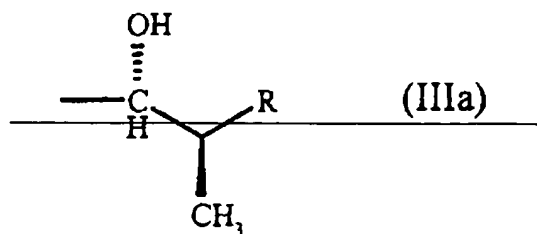
in which:

i) ~~the radicals R₁, R₂, and R₄ to R₁₁, and Z₁, Z₂, and Z₄ to Z₁₁ are defined as for cyclosporin A; or~~

ii) ~~the radicals R₁, R₂, and R₄ to R₁₁, and Z₁, Z₂, and Z₄ to Z₁₁ are defined as for cyclosporin A, with the exception of R₄ and Z₄, which are defined so as to have, at the 4-position, the amino acid 4'-hydroxy-methyleucine; or~~

iii) ~~the radicals R₂ and R₅ to R₁₁, and Z₂ and Z₅ to Z₁₁ are defined as for cyclosporin A; and~~

~~Z₁ is a methyl group and R₄ has the formula:~~



~~_____ in which R is a radical of formula $\text{CH}_2\text{CH}=\text{CHCH}_2\text{R}'$, in which R' is an alkylthio, aminoalkylthio, alkylaminoalkylthio, dialkylaminoalkylthio, pyrimidinylthio, thiazolylthio, N-alkylimidazolylthio, hydroxyalkylphenylthio, hydroxyalkylphenyloxy, nitrophenylamino, or 2-oxopyrimidin-1-yl radical; or~~

~~_____ R is a radical of formula CH_2SAlk in which Alk, is an alkyl group; and~~

~~_____ Z_4 and R_4 are radicals such that there is, at the 4 position, an amino acid-methylleucine or 4'-hydroxy-methylleucine; or~~

~~iv) _____ Z_1 and R_1 are radicals such that there is, at the 1 position, a substituted _____ homothreonine of formula:~~

~~_____ $R_1\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}(\text{OH})\text{CH}(\text{NHCH}_3)\text{COOH}$ _____ (IIIb)~~

~~_____ in which R_1 is n-propyl or propenyl; and~~

~~_____ R_2 and Z_2 are radicals such that there is, at the 2 position, α -aminobutyric acid, valine, norvaline, or threonine; and~~

~~_____ R_4 and Z_4 are radicals such that there is, at the 4 position, N-methyl- γ -hydroxyleucine or N-methyl- γ -acetyloxyleucine; and~~

~~_____ R₅ and Z₅ are radicals such that there is, at the 5 position, valine; and~~

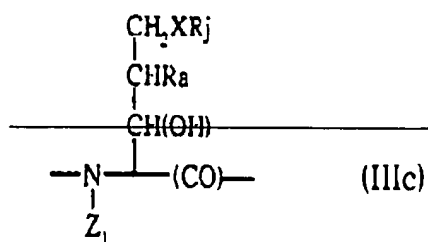
~~_____ R₆, Z₆, R₉, Z₉, R₁₀, and Z₁₀ are radicals such that there is, at the 6, 9, and 10 positions, N-methylleucine; and~~

~~_____ Z₇ and R₇ are radicals such that there is, at the 7 position, alanine; and~~

~~_____ Z₈ and R₈ are radicals such that there is, at the 8 position, D-alanine or D-serine; and~~

~~_____ Z₁₁ and R₁₁ are radicals such that there is, at the 11 position, N-methylvaline; or~~

v) ~~_____ Z₁ and R₁ are radicals such that there is, at the 1 position, an methyl (4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine (MeBmt) radical or a radical having the formula:~~



~~_____ in which R_j is a hydrogen atom or a lower alkyl group, a lower alkenyl, a lower haloalkyl, an aryl, a lower alkyloxy, an alkoxyC₄₋₆alkyl, a hydroxymethyl, a lower alkylthio, an alkylthioC₄₋₆alkyl, a C₄₋₆ mercaptoalkyl, or a heteroaryl;~~

~~it being possible for the aryl and heteroaryl groups to be substituted~~
~~with one or more functional groups chosen from: C₁₋₆ alkyl; C₁₋₆~~
~~alkanoyl; C₁₋₆ haloalkyl; halo; cyano; C₁₋₃ hydroxyalkyl; C₁₋₆~~
~~alkyloxy; C₁₋₆ alkyl S(O)_n, where n = 0, 1, or 2; NR_bCOR₆, in which~~
~~R_b and R₆ independently are H or a C₁₋₆ alkyl, NO₂, NR_bR₆, OR_b,~~
~~CONR_bR₆, COR_b, NR_bCONR_bR₆, NR_bCOR₆, OCOR_b, SCOR_b,~~
~~or OCH₂O; and~~

~~R_a is a lower alkyl; and~~

~~Z₁ is a lower alkyl, a lower phenylalkyl, or an aryl; and~~

~~X is S, SO, SO₂, O, or NR_b; and~~

~~Z₂ and R₂ are radicals such that there is, at the 2 position, the amino acid L-2-~~
~~aminobutyric acid, Norvaline, L-Thr, or the same amino acid as at the 1 position;~~
~~and~~

~~Z₄ and R₄ are radicals such that there is, at the 4 position, the amino acid~~
~~N-methyl-L-leucine; and~~

~~—— Z_5 and R_5 are radicals such that there is, at the 5 position, the amino acid L-valine or norvaline; and~~

~~—— Z_6 and R_6 are radicals such that there is, at the 6 position, the amino acid N-methyl-L-leucine; and~~

~~—— Z_7 and R_7 are radicals such that there is, at the 7 position, the amino acid L-alanine, L-2-aminobutyric acid, or L-phenylalanine; and~~

~~—— Z_8 and R_8 are radicals such that there is, at the 8 position, the amino acid D-alanine or L-alanine; and~~

~~—— Z_9 and R_9 are radicals such that there is, at the 9 position, the amino acid N-methyl-L-leucine or N-methyl-L-valine; and~~

~~—— Z_{10} and R_{10} are radicals such that there is, at the 10 position, the amino acid N-methyl-L-leucine or L-leucine; and~~

~~—— Z_{11} and R_{11} are radicals such that there is, at the 11 position, the amino acid N-methyl-L-valine, L-valine, or L-2-aminobutyric acid; or~~

~~vi) the radicals R_4 to R_{14} and Z_4 to Z_{14} are defined as for cyclosporin A; and~~

~~—— Z₁ and R₁ are radicals such that there is, at the 1 position, the amino acid MeBmt or dihydro-MeBmt; and~~

~~—— Z₂ and R₂ are radicals such that there is, at the 2 position, the amino acid α -aminobutyric acid, threonine, valine, or norvaline; or~~

~~vii) the radicals R₇ to R₁₁ and Z₇ to Z₁₁ are defined as for cyclosporin A; and~~

~~—— Z₁ and R₁ are radicals such that there is, at the 1 position, the amino acid MeBmt, dihydro-MeBmt, or 8'-hydroxy-MeBmt; and~~

~~—— Z₂ and R₂ are radicals such that there is, at the 2 position, the amino acid α -aminobutyric acid, valine, threonine, norvaline, or MeOThr; and~~

~~—— Z₄ and R₄ are radicals such that there is, at the 4 position, the amino acid methyllucine, γ -hydroxy-MeLeu, Melle, MeVal, MeThr, MeAla, Mealle, or MeaThr; and~~

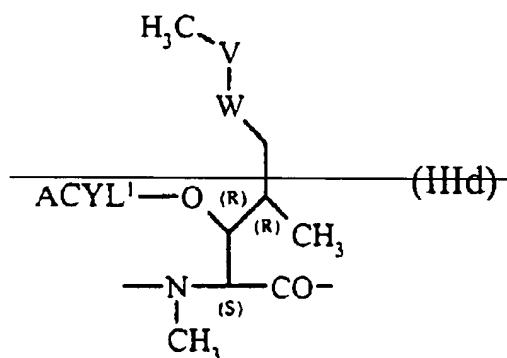
~~—— Z₅ and R₅ are radicals such that there is, at the 5 position, the amino acid valine, Leu, MeVal, or methyllucine; and~~

~~—— Z₆ and R₆ are radicals such that there is, at the 6 position, the amino acid methyllucine, γ -hydroxy-MeLeu, or MeAla;~~

~~provided that, when R_4 and Z_4 are MeLeu, then R_5 and Z_5 are MeVal or methyllucine,
or R_4 and Z_4 are 8'-hydroxy-MeBmt; or~~

~~viii) the radicals R_1 , R_2 , and R_4 to R_{11} , and Z_1 , Z_2 , and Z_4 to Z_{11} define a cyclosporin
in which the 3' carbon of the residue at the 1 position or the β carbon of the residue at
the 2 position is substituted by O-acyl or oxo; and~~

~~_____ Z_1 and R_1 are radicals such that there is, at the 1 position, a residue of formula~~



~~_____ in which $V-W$ is CH_2-CH_2 or trans $CH=CH$ and $ACYL^1$ is an acyl~~

~~_____ group; and~~

~~_____ Z_2 and R_2 are radicals such that there is, at the 2 position, an amino acid~~

~~α -aminobutyric acid, valine, threonine, norvaline, or a β -O-acylated α -amino acid;~~

~~and~~

~~—— Z₅ and R₅ are radicals such that there is, at the 5 position, an amino acid valine or norvaline when there is simultaneously an amino acid norvaline at the 2 position; and~~

~~—— Z₈ and R₈ are radicals such that there is, at the 8 position, an amino acid D-alanine or a β -O-acylated or β -hydroxylated α -amino acid having the D-configuration; and~~

~~—— the radicals at the 4, 6, 7, and 9 to 11 positions are defined as for cyclosporin A; and~~

~~one or more hydroxyl groups and optionally one or more non-methylated nitrogen atoms at the α position and optionally any other deprotonatable acidic group present in said formula (II) are optionally deprotonated or in the protected form.~~

5. (Original) The process according to claim 1, in which said hexamethyldisilazane metal salt is a hexamethyldisilazane alkali metal salt.

6. (Original) A process according to claim 5, in which said hexamethyldisilazane metal salt is chosen from the hexamethyldisilazane lithium salt, the hexamethyldisilazane sodium salt, and the hexamethyldisilazane potassium salt.

7. (Original) The process according to claim 6, in which said hexamethyldisilazane metal salt is used in an amount ranging from 20 to 30 molar equivalents.

8. (Currently Amended) The process according to claim 1 2, in which, when the treatment of the cyclosporin is carried out in the presence of a metal halide, said metal halide is chosen from lithium chloride, caesium chloride, caesium fluoride, cuprous chloride, and mercuric chloride.

9. (Original) The process according to claim 8, in which, when said metal halide is caesium chloride or lithium chloride, it is used in an amount ranging from 2 to 8 molar equivalents.

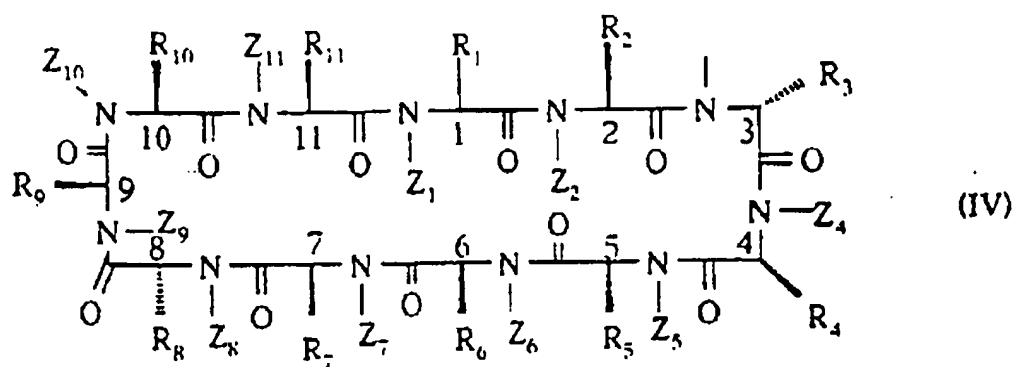
10. (Original) The process according to claim 9, in which the treatment of the cyclosporin is carried out in an aliphatic or cyclic ether, an aromatic hydrocarbon, or a mixture of these solvents.

11. (Original) The process according to claim 10, in which the treatment of the cyclosporin is carried out at a temperature ranging from -40°C to 0°C.

12. (Original) The process according to claim 11, in which the treatment of the cyclosporin is carried out with a ratio (weight/weight) of cyclosporin involved with respect to the total weight of the solution which is less than or equal to 10%.

13. (Currently Amended) A process for preparing a cyclosporin derivative substituted at the 3-position, said process comprising preparing a polyanion by treating a cyclosporin with a hexamethyldisilazane metal salt, optionally in the presence of a metal halide, adding an electrophilic agent to said treated cyclosporin, and, optionally converting the product of said addition to a salt, ~~wherein the hydroxyl-radicals, if any, present on the cyclosporin which may possibly interfere with the reaction are protected before said treatment and then the protective radicals are removed, after said treatment.~~

14. (Currently Amended) The process according to claim 13, in which at least one obtained cyclosporin derivative substituted at the 3-position has the formula:



in which:

1) ~~the radicals R₁ to R₁₁ and Z₁ to Z₁₁ are as defined in claim 4 in i) and R₃ is a radical -S-Alk-R° in which:~~

~~Alk is an alkylene radical comprising from 2 to 6 straight or branched chain carbon atoms or a cycloalkylene radical comprising from 3 to 6 carbon atoms; and~~

~~R° is~~

~~a carboxyl or alkylloxycarbonyl radical; or~~

~~an NG₁G₂ radical in which G₁ and G₂, which are identical or different, are each~~

~~a hydrogen atom; or~~

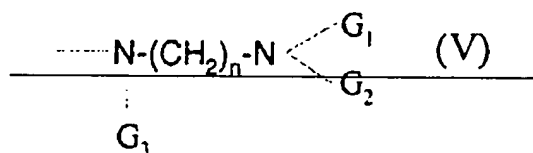
~~a phenyl, cycloalkyl (C₃₋₆), alkenyl (C₂₋₄), or alkyl radical, each of which is optionally substituted by a halogen atom, an alkylloxy, alkylloxycarbonyl, amino, alkylamino, or dialkylamino radical; or~~

~~a benzyl radical or a saturated or unsaturated heterocyclyl radical comprising 5 or 6 ring members and from 1 to 3 heteroatoms; or~~

~~G₁ and G₂ form, with the nitrogen atom to which they are attached, a saturated or unsaturated heterocycle comprising from 4 to 6 ring members which can comprise another heteroatom chosen from~~

~~nitrogen, oxygen, and sulphur and which is optionally substituted~~
~~by alkyl, phenyl, or benzyl; or~~

~~a radical of formula:~~



~~in which G₁ and G₂ are defined as above, G₃ is a hydrogen atom or an~~
~~alkyl radical, and n is an integer from 2 to 4, the alkyl portions or radicals~~
~~defined above are straight or branched and comprise from 1 to 4 carbon~~
~~atoms; or~~

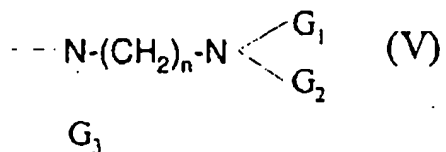
2) ~~the radicals R₁ to R₁₁ and Z₁ to Z₁₁ are as defined in claim 4 in ii) and, except for~~
R₃, which is -S-CH₃ or a radical -S-Alk-R° in which:

Alk is an alkylene radical comprising from 2 to 6 straight- or branched-chain
carbon atoms or a cycloalkylene radical comprising from 3 to 6 carbon atoms;
and

R° is

a hydroxyl, carboxyl, or alkyloxycarbonyl radical; or

an -NG₁G₂ radical or a radical of formula:



as defined above; or

~~3) the R₁ to R₁₁ and Z₁ to Z₁₁ radicals are as defined in claim 4 in iii) and R₃ a radical of structure S-Alk-R° in which:~~

~~Alk is an alkylene radical comprising from 2 to 6 straight or branched chain carbon atoms or a cycloalkylene radical comprising from 3 to 6 carbon atoms; and~~

~~R° is~~

~~a hydrogen atom or a hydroxyl, carboxyl, or alkyloxycarbonyl radical; or~~

~~an -NG₁G₂ radical in which G₁ and G₂, which are identical or different, are each~~

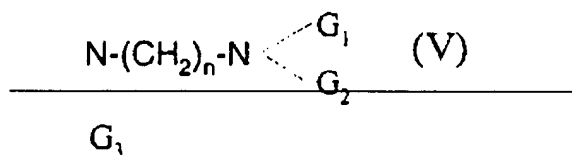
~~a hydrogen atom; or~~

~~_____ a phenyl, cycloalkyl (C₃₋₆), or alkyl radical, each of which is _____
_____ optionally substituted by a halogen atom, or an alkyloxy, _____
_____ alkyloxycarbonyl, amino, alkylamino, or dialkylamino radical; or _____~~

~~_____ a benzyl radical or a saturated or unsaturated heterocyclyl radical _____
_____ comprising 5 or 6 ring members and from 1 to 3 heteroatoms; or _____~~

~~_____ G₄ and G₂ form, with the nitrogen atom to which they are attached, _____
_____ a 5- or 6-membered heterocycle which can comprise another _____
_____ heteroatom chosen from nitrogen, oxygen, and sulphur and which _____
_____ is optionally substituted by alkyl; or _____~~

~~_____ a radical of formula: _____~~



~~_____ as defined above; or _____~~

4) the radicals R₄ to R₁₄ and Z₁ to Z₁₄ are as defined in claim 4 in iv) and R₃ is a radical chosen from:

~~straight or branched alkyl (C₂₋₆), alkenyl, or alkynyl, each of which is optionally substituted by a hydroxyl, amino, C₁₋₄ alkylamino, C₁₋₃ dialkylamino, alkyloxy, or acyloxy group;~~

~~COOG₄ or CONHG₄, in which G₄ is a straight or branched alkyl comprising from 1 to 4 carbon atoms;~~

~~Y-G₅, in which Y is S or O, and G₅ is a straight or branched C₁ to C₄ alkyl, a straight or branched alkenyl, or a straight or branched alkynyl, and in which, if Y is S, G₅ can also be an aryl or a heteroaryl;~~

~~a halo or cyano group; and~~

~~CHG₆G₇, in which G₆ is a hydrogen atom or a methyl, ethyl, or phenyl group and G₇ is a hydrogen atom or a hydroxyl, halo, amino, C₁₋₄ alkylamino, C₁₋₄ dialkylamino, acyloxy, *t*-butoxycarbonylaminoethoxyacetyloxy, or alkyloxycarbonyl group; or~~

5) ~~the radicals R₁ to R₁₄ and Z₁ to Z₁₄ are as defined in claim 4 in v) and R₃ is a radical such that there is, at the 3 position, an α -(methylmercapto)sarcosyl or N-methyl-D-alanyl residue; or~~

6) ~~the radicals R₁ to R₁₁ and Z₁ to Z₁₁ are as defined in claim 4 in vi) and R₃ is a~~
~~G₁₋₆alkyl, haloG₁₋₆alkyl, hydroxyG₁₋₆alkyl, mercaptoG₁₋₆alkyl, aminoG₁₋₆alkyl,~~
~~G₂₋₅alkoxycarbonylamino(C₁₋₄alkyl), nitroG₁₋₆alkyl, cyanoG₁₋₅alkyl, G₁₋₆alkoxy(G₁₋₆alkyl),~~
~~G₁₋₆alkylthio (G₁₋₆alkyl), G₂₋₇alkanoyloxy(G₁₋₆alkyl), G₂₋₇diazoalkanoyloxy(G₁₋₆alkyl),~~
~~carboxy(G₁₋₆alkyl), G₂₋₇alkoxycarbonyl(G₁₋₆alkyl), aminocarbonyl(C₁₋₄alkyl),~~
~~aminocarbonyloxy(C₁₋₄alkyl), amino(G₁₋₄alkanoyloxy)(G₁₋₄alkyl),~~
~~amino(G₂₋₈alkoxycarbonyl)(G₁₋₄alkyl), G₂₋₇alkylcarbonyl, G₂₋₇alkoxycarbonyl,~~
~~G₁₋₆alkylthio, hydroxyG₁₋₆alkylthio, G₁₋₆alkoxy(G₁₋₆alkylthio),~~
~~G₂₋₁₁alkanoyloxy(G₂₋₄alkylthio), G₂₋₁₁alkanoyloxy(G₂₋₄alkylsulphinyl),~~
~~G₂₋₁₁alkanoyloxy(G₂₋₄alkylsulphonyl), aminocarbonyloxy(G₂₋₄alkylthio),~~
~~G₂₋₁₁aminoalkanoyloxy(G₂₋₄alkylthio), aminocarbonyloxy(G₂₋₄alkylsulphinyl),~~
~~aminocarbonyloxy(G₂₋₄alkylsulphonyl), aminoalkanoyloxy(G₂₋₄alkylsulphinyl),~~
~~aminoalkanoyloxy(G₂₋₄alkylsulphonyl), aminocarbonyl, C₃₋₆alkenyl, C₃₋₆alkynyl,~~
~~haloC₃₋₆alkenyl, haloC₃₋₆alkynyl, hydroxyC₃₋₆alkenyl, aryl(G₁₋₆alkyl), hydroxylated~~
~~aryl(G₁₋₆alkyl), aryl(C₃₋₆alkenyl), aryl(C₃₋₆alkynyl), hydroxylated aryl(C₃₋₆alkenyl),~~
~~hydroxylated aryl(C₃₋₆alkynyl), arylthio, heteroarylthio, aryl(G₂₋₅alkoxycarbonylamino)(C₁₋~~
~~4alkyl), halo, or cyano radical, or a radical of formula Q-(CH₂-CH₂-O)_n-CO-O-CH₂-, in~~
~~which n is 1, 2, or 3 and Q is amino; or~~

7) ~~the radicals R₁ to R₁₁ and Z₁ to Z₁₁ are as defined in claim 4 in vii) and R₃ is a~~
~~radical such that there is, at the 3 position, an amino acid D-MeAla; or~~

~~8) — the radicals R_1 to R_{11} and Z_1 to Z_{11} are as defined in claim 4 in viii) and R_3 is a radical such that there is, at the 3-position, an α -amino acid which is N-methylated at the α -position and which has the D-configuration.~~

15. (Withdrawn) A method for preventing or treating a retrovirus infection or an associated syndrome, comprising administering to a mammal in need or desire thereof an effective amount of a cyclosporin derivative as defined in claim 14 in 1), 2), 3), 4), or 7).

16. (Withdrawn) The method of claim 15, in which the retrovirus infection is AIDS (acquired immunodeficiency syndrome).

17. (Withdrawn) A method for treating a chronic inflammatory disease or an autoimmune disease, comprising administering to a mammal in need or desire thereof an effective amount of a cyclosporin derivative as defined in claim 14 in 5).

18. (Withdrawn) A method for preventing or treating an autoimmune disease or preventing rejection of a transplanted organ, comprising administering to a mammal in need or desire thereof an effective amount of a cyclosporin derivative as defined in claim 14 in 6) or 8).

19. (Withdrawn) A method for treating inflammation, comprising administering to a mammal in need or desire thereof an effective amount of a cyclosporin derivative as defined in claim 14 in 6) or 8).

20. (Withdrawn) The method of claim 19, in which the inflammation is an arthritis or a rheumatic disease.

21. (Withdrawn) A method for treating schistosomiasis, filariasis, leishmaniasis, coccidioidomycosis, or malaria, comprising administering to a mammal in need or desire thereof an effective amount of a cyclosporin derivative as defined in claim 14 in 6) or 8).

22. (Cancelled) The process according to claim 1, wherein when R_i in formula (IIIb) is propenyl, the double bond exhibits a trans configuration.

23. (Currently Amended) The process according to claim 13, wherein said cyclosporin derivative substituted at the 3-position is chosen from:

~~[(R)-2-aminoethylthio-Sar]3-cyclosporin A;~~

~~[(R)-2-(N-methylamino)ethylthio-Sar]3-cyclosporin A;~~

~~[(R)-2-(N-ethylamino)ethylthio-Sar]3-cyclosporin A;~~

~~[(R)-2-(N-isopropylamino)ethylthio-Sar]3-cyclosporin A;~~

~~[(R)-2-(N-t-butylamino)ethylthio-Sar]3-cyclosporin A;~~

~~[(R)-2-(N-phenylamino)ethylthio-Sar]3-cyclosporin A;~~

~~[(R)-2-(N-benzylamino)ethylthio-Sar]3-cyclosporin A;~~
~~[(R)-2-(N-methyl-N-ethylamino)ethylthio-Sar]3-cyclosporin A;~~
~~[(R)-2-(N-methyl-N-allylamino)ethylthio-Sar]3-cyclosporin A;~~
~~[(R)-2-(N-methyl-N-phenylamino)ethylthio-Sar]3-cyclosporin A;~~
~~[(R)-2-(N,N-diisopropylamino)ethylthio-Sar]3-cyclosporin A;~~
~~[(R)-2-(N,N-diallylamino)ethylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-aminopropylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N-methylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N-ethylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N-isopropylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N-t-butylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N-phenylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N-benzylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N-methyl-N-ethylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N-methyl-N-isopropylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N-methyl-N-t-butylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N-methyl-N-allylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N-methyl-N-phenylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N-methyl-N-benzylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N,N-diethylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N,N-diisopropylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(N,N-diallylamino)propylthio-Sar]3-cyclosporin A;~~
~~[(R)-3-(1-piperidyl)propylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-aminobutylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N-methylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N-ethylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N-isopropylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N-t-butylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N-phenylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N-benzylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N-methyl-N-ethylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N-methyl-N-isopropylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N-methyl-N-t-butylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N-methyl-N-allylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N-methyl-N-phenylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N-methyl-N-benzylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N,N-dimethylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N,N-diethylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N,N-diisopropylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(N,N-diallylamino)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-4-(1-piperidyl)butylthio-Sar]3-cyclosporin A;~~

~~[(R)-2-amino-2-methylpropylthio-Sar]3-cyclosporin A;~~

~~[(R)-2-(N,N-dimethylamino)-2-methylpropylthio-Sar]3-cyclosporin A;~~

~~[(R)-2-(N,N-diethylamino)-2-methylpropylthio-Sar]3-cyclosporin A;~~

~~[(R)-2-(1-piperidyl)-2-methylpropylthio-Sar]3-cyclosporin A;~~

~~[(R)-3-amino-3-methylbutylthio-Sar]3-cyclosporin A;~~

~~{{(R)-3-(N,N-dimethylamino)-3-methylbutylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-3-(N,N-diethylamino)-3-methylbutylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-3-(1-piperidyl)-3-methylbutylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-2-(1-morpholino)ethylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-2-(1-azetidino)ethylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-2-[1-(4-methylpiperazino)]ethylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-2-[1-(4-phenylpiperazino)]ethylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-2-[1-(4-benzylpiperazino)]ethylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-2-[1-(4-methyl-1,2,3,6-tetrahydropyridyl)]ethylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-2-[1-(4-phenyl-1,2,3,6-tetrahydropyridyl)]ethylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-3-(1-morpholino)propylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-3-(1-azetidino)propylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-3-[1-(4-methylpiperazino)]propylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-3-[1-(4-phenylpiperazino)]propylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-3-[1-(4-benzylpiperazino)]propylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-3-[1-(4-methyl-1,2,3,6-tetrahydropyridyl)]propylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-3-[1-(4-phenyl-1,2,3,6-tetrahydropyridyl)]propylthio-Sar}3-cyclosporin-A;~~
~~{{(R)-2-aminoethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin-A;~~
~~{{(R)-2-(N-methylamino)ethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin-A;~~
~~{{(R)-2-(N-ethylamino)ethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin-A;~~
~~{{(R)-2-(N-isopropylamino)ethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin-A;~~
~~{{(R)-2-(N-t-butylamino)ethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin-A;~~
~~{{(R)-2-(N-phenylamino)ethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin-A;~~

~~[(R)-2-(N-benzylamino)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-2-(N-methyl-N-ethylamino)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-2-(N-methyl-N-isopropylamino)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-2-(N-methyl-N-tert-butylamino)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-2-(N-methyl-N-allylamino)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-2-(N-methyl-N-phenylamino)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-2-(N-methyl-N-benzylamino)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-2-(N,N-diethylamino)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-2-(N,N-diisopropylamino)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-2-(N,N-diallylamino)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-2-(1-piperidyl)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-3-aminopropylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-3-(N-methylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-3-(N-ethylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-3-(N-isopropylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-3-(N-tert-butylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-3-(N-phenylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-3-(N-benzylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-3-(N-methyl-N-ethylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-3-(N-methyl-N-isopropylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-3-(N-methyl-N-t-butylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-3-(N-methyl-N-allylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~[(R)-3-(N-methyl-N-phenylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-3-(N-methyl-N-benzylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-2-(N,N-dimethylamino)ethylthio-Sar]³-[4'-hydroxy-MeLeu]⁴-cyclosporin A;~~

~~[(R)-3-(N,N-diethylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-3-(N,N-diisopropylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-3-(N,N-diallylamino)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-3-(1-piperidyl)propylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-aminobutylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N-methylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N-ethylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N-isopropylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N-t-butylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N-phenylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N-benzylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N-methyl-N-ethylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N-methyl-N-isopropylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N-methyl-N-t-butylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N-methyl-N-allylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N-methyl-N-phenylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N-methyl-N-benzylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N,N-dimethylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N,N-diethylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N,N-diisopropylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~[(R)-4-(N,N-diallylamino)butylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~{{(R)-4-(1-piperidyl)butylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-2-amino-2-methylpropylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-2-(N,N-dimethylamino)-2-methylpropylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-2-(N,N-diethylamino)-2-methylpropylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-2-(1-piperidyl)-2-methylpropylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-3-amino-3-methylbutylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-3-(N,N-dimethylamino)-3-methylbutylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-3-(N,N-diethylamino)-3-methylbutylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-3-(1-piperidyl)-3-methylbutylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-2-(1-morpholino)ethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-2-(1-azetidino)ethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-2-[1-(4-methylpiperazino)]ethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-2-[1-(4-phenylpiperazino)]ethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-2-[1-(4-benzylpiperazino)]ethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-2-[1-(4-methyl-1,2,3,6-tetrahydropyridyl)]ethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-2-[1-(4-phenyl-1,2,3,6-tetrahydropyridyl)]ethylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-3-(1-morpholino)propylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-3-(1-azetidino)propylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-3-[1-(4-methylpiperazino)]propylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~
~~{{(R)-3-[1-(4-phenylpiperazino)]propylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~{{(R)-3-[1-(4-benzylpiperazino)]propylthio-Sar}3-[4'-hydroxy-MeLeu]4-cyclosporin A;~~

~~{{(R)-3-[1-(4-methyl-1,2,3,6-tetrahydropyridyl)]propylthio-Sar}3-[4'-hydroxy-MeLeu]4-~~
cyclosporin A; and

~~{{(R)-3-[1-(4-phenyl-1,2,3,6-tetrahydropyridyl)]propylthio-Sar}3-[4'-hydroxy-MeLeu]4-~~
cyclosporin A.

24. (New) The process of claim 13, in which at least one hydroxyl radical present on said cyclosporin that interferes with the treating reaction is protected before said treatment with a protective radical and then the protective radicals are removed after said treatment.